Neural Sensitivities in Disruptive Mood Dysregulation Disorder (DMDD):
Using the Reinforcement Sensitivity Theory of Personality and Selected Research Domain Criteria in Order to Understand DMDD

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Abstract

This paper provides a theoretical and empirical analysis of a recently conceptualized childhood disorder; disruptive mood dysregulation disorder (DMDD). The reinforcement sensitivity theory of personality (RST) is presented as a model for understanding DMDD. Model overlap with the research domain criteria (RDoC), a contemporary framework for research in the field of psychology, is noted, specifically in the domains of threat, reward and cognition. A differential diagnostic analysis compares DMDD to bipolar disorder, ADHD, oppositional defiant disorder, anxiety and depression. In line with the RST, DMDD is proposed to be a disorder of combined neural bottom-up sensitivity, which may compromise top-down control. Research proposals for how to further the understanding of DMDD in line with the RST model, is provided. Results from neuropsychological testing are mixed, showing both deficits and normative performance compared to other clinical groups and healthy controls. fMRI, however, shows increased bottom-up reactivity and compensatory prefrontal control. The anterior cingulate cortex (ACC) is suggested as a switchboard between RST system, and an ACC-mediated visual attention deficit is hypothesized. Furthermore, more ecologically relevant studies, studies on tasks requiring both hot and cool cognition, larger and more DMDD-specific experimental groups and the use of sophisticated fMRI technology, are essential in further delineating the specific features of DMDD and the possible interplay between RST dimensions in childhood irritability.
Neural Sensitivities in Disruptive Mood Dysregulation Disorder (DMDD):
Using the Reinforcement Sensitivity Theory of Personality and Selected Research Domain Criteria in Order to Understand DMDD

Disruptive mood dysregulation disorder (DMDD) is a recently conceptualized childhood psychiatric disorder, first featured in the last edition of the American Psychological Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-5, APA, 2013). Core diagnostic criteria for DMDD are persistently irritable mood, and together with this, frequent and severe temper outbursts (APA, 2013). The severity of the behavioral outcome of the disorder both short-term (Copeland, Angold, Costello, & Egger, 2013) and long-term (Copeland, Shanahan, Egger, Angold, & Costello, 2014; Stringaris, 2011), puts pressure on the scientific community to find better conceptual understanding and treatment models to aid the children and their families suffering from this disorder.

The Children with Severe Emotional Dysregulation Study at the Nic Waal Institute, a child and youth outpatient clinic, and Ullevål Hospital inpatient clinic in Oslo, is an ongoing clinical study on childhood irritability, with specific focus on the DMDD diagnosis. Throughout this paper there will be quotes from clinical interviews, using an adapted version of the Kiddie-SADS-PL (original version by Kaufman et al., 2016). The following quote is an excerpt from a clinical interview at the Nic Waal Institute.

Has frequent rage outbursts, and a persistent irritable mood, mostly at home. Rage outbursts are unpredictable and can come without precaution. However, upon situations with behavioral demands, when transition from one activity to another is required, and when parents are not calm when giving an instruction, rages are more frequently displayed.

(Information provided by parents of boy, age eight, diagnosed with DMDD)

As seen in the clinical quote above, having a child with DMDD puts massive strain on the family and requires particularly sensitive parenting strategies. Meeting these predictable and unpredictable rages is arguably a tiring process in hectic everyday lives, and family functioning is threatened. The children exhibiting these behavioral patterns seem to suffer. Appropriate and effective treatment for childhood irritability is under development, and dependent on the understanding of predispositional and maintaining factors (Brotman, Kircanski, Stringaris, Pine, & Leibenluft, 2017; Leibenluft, 2017). The Children with Severe Emotional Dysregulation Study is a longitudinal study, attempting a more sophisticated understanding of DMDD. This research will ultimately guide practitioners in their work helping these children and families. The present paper is a theoretical contribution, and an
attempt to provide a neuropsychological model to be used in the study of children with DMDD.

Clinical Presentation

Serious emotional and behavioral dysregulation, as well as chronic irritability, are frequent reasons for child and youth referral to mental health care. About a third of all referrals to clinic present with morbid irritability (Stringaris, 2011). This makes it a frequent and significant challenge for practitioners. Irritability is a diagnostic criterion for several childhood disorders (APA, 2013). A study by Mayes et al. (2015) found that several diagnoses often presented with DMDD symptoms. For example, 56% of autism spectrum diagnoses and 39% with attention deficit hyperactivity disorder (ADHD)-combined type also had concurrent (“often or very often”) DMDD symptoms. Furthermore, 91% with DMDD diagnosis also presented with oppositional defiant disorder (ODD), and 79% with ODD presented with DMDD (Mayes et al., 2015). Anxiety and depression are also prominent co-existing conditions to DMDD (Copeland et al., 2013). It is clear that the boundaries between clinical disorders are not always clear-cut, and there seems to be many etiologies to irritability as a presenting feature. Clinical judgement is complicated due to overlap of diagnostic categories and symptoms. Due to the understanding of DMDD as a separate disorder (APA, 2013) the focus in this paper will be on DMDD.

From the above presentation of the diagnostic criteria of DMDD as well as the data on comorbidities, one may deduce that DMDD is a disorder with internalizing and externalizing features. Internalizing is expressed in anxiety, depression, and withdrawn behavior. Externalizing is represented in behavioral/disruptive disorders and impulsive and often maladaptive actions. Children with DMDD are on the internalizing spectrum, due to mood symptoms. Anger outbursts qualify as externalizing behavior. Due to high comorbidity rates, and commonalities in behavioral expression with other childhood disorders, there is need for more knowledge about the specifics that differentiate DMDD from other clinical presentations. Research findings surrounding overlapping and separate features of DMDD and other disorders are of interest to the understanding of DMDD specifically. Whether DMDD internalizing and externalizing features interact, and possibly provide consistent results on cognitive measures, is an area of interest. These questions regarding DMDD presentation will be treated throughout this paper. Child interaction with social environment is an important topic when symptom load is severe. However, in this paper, the focus will be specifically on neural and cognitive explanations of irritability, regardless of possible causal explanations existing in environmental factors.
Research Focus and Questions in the Current Paper

There has been criticism with regard to the validity of clinical diagnostic systems, depending as they do on symptom presentation, rather than being based on underlying systems neurobiology and behavior (Cuthbert & Insel, 2013). The National Institute of Mental Health’s response to these challenges was the development of the year 2009 formulation of the research domain criteria (RDoC, NIMH, 2019). The intent was to establish domains of preferential and integrative research effort in order to understand behavior, from normal to clinical range (Cuthbert & Insel, 2013). The RDoC strategies include finding contributing neurobiological structures and functioning as a part of the venture in understanding human behavior (Cuthbert & Insel, 2013). Meyers, DeSerisy and Roy (2017) proposed the use of RDoCs in furthering the understanding of mechanisms of dysfunction in children with DMDD.

The reinforcement sensitivity theory of personality (RST, Corr, 2008), is a neuropsychological model that understands psychopathology as a correlate of extreme sensitivities and interactions of separate neural systems underlying behavioral dispositions. This model may be utilized as a theoretical framework to understand DMDD presentation. There is significant overlap in RDoC constructs and RST model dimensions. In this paper an analysis of how to understand DMDD in a combined RST and RDoC framework will be provided. While the theoretical development of the RST has roots in early animal research as well as early discussion surrounding what constitutes personality (e.g. Gray, 1970; 1975; 1991), the overlap of RST and RDoC constructs makes this analysis a modern and up-to-date undertaking. There will not be thorough treatment of the RDoC, as it is a framework for research endeavors resulting in many separate traditions. However, central concepts from the RDoC that line up with RST will be noted throughout this text.

The next section will contain a description of the basic framework of the RST model and its overlap with the RDoC. Furthermore its relevance to understanding psychopathology will be argued. After this there will be an analysis of how DMDD differs neurally from other diagnoses, in order to clarify clinical boundaries and commonalities. Successively, an analysis of the understanding of DMDD in light of RST and RDoC relevant research will be performed. The aim in using this model is to provide a holistic understanding of DMDD, so that contributions of separate and coordinated neural systems can be argued. Limitations and strengths of using the model will be discussed, along with limitations to the current theoretical discussion. The ultimate aim of this paper is to show how the RST can be used to provide a conceptual and theoretical framework for future studies on DMDD, and to give some
suggestions on how to proceed with this.

In summary, the research questions of this paper are:

- How can one understand DMDD in light of the reinforcement sensitivity theory of personality and the research domain criteria?
- How does DMDD present in a neurally and behaviorally different manner from other childhood disorders?
- Using the RST/ RDoC understanding, can one provide a specific neural and cognitive profile for children with DMDD? What is the role of the anterior cingulate cortex?
- What are the limitations in the RST model in general and with regards to explaining DMDD, and what research is needed to further the understanding of DMDD in a RST model/ RDoC framework?

The Reinforcement Sensitivity Theory Conceptual Starting Point

This first section will provide a description of the theoretical background which will be used in the analysis of DMDD, including an outline of the RDoC and the RST.

The Research Domain Criteria

One of the NIMH RDoC strategic goals is the integration of genetic, neurobiological, environmental, and experiential components of disorders (Cuthbert & Insel, 2013). The presentation here will confine itself to neuropsychology, fMRI and self-report. The RDoC is a comprehensive guideline from the lead American federal agency for research on mental disorders. Each concept in every domain is retrieved from and further guides varied research traditions. Several of the RDoC concepts are relevant to the RST. This makes the RST a model worth exploring when trying to understand the clinical presentations of disorders. Table 1 below provides an oversight over the RDoC. Throughout this paper the domains of reward and threat will be treated, along with some research on the cognitive systems.

| Table 1 |

NIMH Research Domain Criteria (RDoC) |

<table>
<thead>
<tr>
<th>Negative valence domain</th>
<th>Positive valence systems</th>
<th>Cognitive systems</th>
<th>Systems for social processes</th>
<th>Arousal/ modulatory systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute fear</td>
<td>Approach motivation</td>
<td>Attention</td>
<td>Affiliation/ Attachment</td>
<td>Arousal</td>
</tr>
<tr>
<td>Potential threat</td>
<td>Initial responsiveness to reward</td>
<td>Perception</td>
<td>Social communication</td>
<td>Biological rhythms</td>
</tr>
<tr>
<td>Sustained threat</td>
<td>Sustained response</td>
<td>Working memory</td>
<td>Perception and</td>
<td>Sleep-wake</td>
</tr>
</tbody>
</table>

Table 1
<table>
<thead>
<tr>
<th>siveness to reward</th>
<th>understanding-self</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss</td>
<td>Reward learning</td>
</tr>
<tr>
<td>Frustrative nonreward</td>
<td>Habit</td>
</tr>
</tbody>
</table>

Table 1 is adapted from Cuthbert and Insel (2013).

**RST Basics**

The reinforcement sensitivity theory of personality is the result of a joined research effort based upon the empirical and conceptual foundations laid by J. A. Gray (1970; 1975; 1991) and co-workers (e.g. Gray & McNaughton, 2000; Corr, 2008). The RST provides a conceptual understanding of neural systems hypothesized to have different sensitivities in different individuals, each system serving an integrated function. Evolutionary thinking serves as its basis, and it was initially developed from animal research. Neuroimaging technology has provided human neural activation data to add layers of understanding to the model. The latest comprehensive theoretical treatment on aspects of the theory was in 2000/2003 (Gray & McNaughton, 2000). Efforts have also been made to compile relevant research in chapters to provide insight and inspiration for future research (Corr, 2008). An extension of the model was suggested by Carver (2005), and reviewed by Kennis, Rademaker and Geuze (2013).

Neural systems are defined as neural structures that interlink, and serve a common functional purpose (Woolsey, 2019). Research on neural responsivity is state-dependent, as it is studied in behavioral paradigms. The link to personality rests on the assumption that through research on state motivations, one can examine trait tendencies (Corr & Krupić, 2017). RST self-report questionnaires have provided data on trait functioning (e.g. Carver & White, 1994; Muris, Meesters, de Kanter, & Timmermann, 2005). However, self-report studies will not be used in this paper in order to explain behavior due to possible confounding effects (see e.g. Eisenberger, Lieberman, & Satpute, 2005). It is assumed in RST that stimuli elicit states of positive or negative valence, which create “goal representations” and guide instrumental behavior (Gray, 1991). The underlying neural systems treating these goals are assumed to be nomothetic. Individual variability in responsivity lies within the accumulation of experience and sensitivities of systems (Gray, 1975).

The RST is a learning theory in that it bases its conceptualization on the study of stimuli - response (S-R) connections. It is also a biological theory in that is has studied the underlying neurology of these S-R connections. A frequently used psychological term for
human behavioral pattern is the concept of temperament. Temperament is seen as a combination of biologically based factors that manifest in a pattern of emotional reactions (Clark & Watson, 2008). Temperament is a trait factor, which should involve some genetic impact, as well as some predictability in individual functioning. Due to evidence that difficulties may be of lasting character for children with severe irritability (Copeland et al., 2014; Stringaris, 2011), it is possible that one can partly conceptualize the behavioral pattern observed in such children as a phenotypical expressions of underlying temperament. While the concept of temperament is often used in the study of children, personality forms in the interplay between biological frameworks and learning experiences (Farrell, Brook, Dane, Marini, & Volk, 2014). The RST is a theory of personality. However the concepts of temperament and personality can be used intermittently, as the RST uses neural responsivity explanations to behavior patterns. Temperament is here understood as a constitution based on neural sensitivities. Each system will be presented next, in line with Kennis et al.’s (2013) suggestion that the RST is best understood with four dimensions.

The RST Systems

Table 2 provides a preliminary description of the RST dimensions.

Table 2

The Four Systems of the Reinforcement Sensitivity Theory of Personality

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Emotion</th>
<th>Correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fight-flight-freeze system</td>
<td>Fear</td>
<td>freezing, panic, attack</td>
</tr>
<tr>
<td>Behavioral inhibition system</td>
<td>Anxiety</td>
<td>rumination, worry, arousal</td>
</tr>
<tr>
<td>Behavioral approach system</td>
<td>Elation</td>
<td>optimism, impulsivity, reward</td>
</tr>
<tr>
<td>Constraint/ effortful control</td>
<td>Determination</td>
<td>controlled behavior, volition</td>
</tr>
</tbody>
</table>

The Fight-Flight-Freeze System (FFFS)

The FFFS is a system responding to danger (Gray & McNaughton, 2000). Fear is the associated emotion of this system, and freezing or panic is the behavioral response. Observationally, freezing is often seen preceding explosive attack or flight (Gray & McNaughton, 2000). Larsen and Buss (2005, in Kennis et al., 2013), claimed that people high in FFFS tend to be irritable, tense and nervous, and have low self-esteem. Aspects of OCD, panic and phobias are believed to be related to high FFFS activation (McNaughton & Corr, 2004).
**The Behavioral Approach System (BAS)**

The BAS is hypothesized to be an appetitive system, motivated by reward (Corr, 2008; Corr & Krupić, 2017; Gray, 1975; 1991). Termination or omission of punishment is also a motivational signal to the BAS (Corr, 2008; Gray, 1991). Attractors can be any item, place or state the individual is motivated to approach (Corr, 2008). Personality-wise, BAS measures have been found to correlate with e.g. extraversion (Muris et al., 2005), and the personality factors optimism, impulsivity and orientation towards reward (Corr, 2008). However, BAS has also been found to a certain degree to be related to childhood externalizing symptoms (Muris et al., 2005). Corr and Krupić (2017) wrote that BAS at normal levels is related to positive outcomes, while at extreme sensitivities BAS is related to sensation-seeking and high-risk behaviors.

The goal-persistent regulation of behavior in terms of situational prerequisites, as well as cognitions about various behaviors to achieve subgoals and main goals are included in the hypothesized function of this system (Gray, 1991). Gray (1991) gave a short, computational account of the BAS. Drawing upon research on the motor programming system, which is conceptually the same as the BAS, he distinguished between the caudate and the accumbens motor systems. The caudate system has been found to be activated at each step towards reaching a goal, while the accumbens system is responsible for the switching between steps (Gray, 1991). Excitatory and inhibitory projections are involved. The prefrontal cortex (PFC) is hypothesized to coordinate this activity, however the pathways of its influence is not treated in Gray’s (1991) chapter, and only tentatively in more contemporary accounts (e.g. McNaughton & Corr, 2004), leaving open questions regarding its hypothetical role in BAS-related activity.

**The Behavioral Inhibition System (BIS)**

The BIS is a system conceptualized to handle conflict between the FFFS and the BAS, or also between goals of equal valence (Gray & McNaughton, 2000; McNaughton & Corr, 2004). Phenomenologically BIS is experienced as rumination and worry (Corr, 2008). BIS as a trait is related to neuroticism, behavioral inhibition (Gray & McNaughton, 2000), increased arousal (Corr, 2008) and decreased threat threshold/ generally oversensitive alerting and orienting of attention (Pacheco-Unguetti, Acosta, Callejas, & Lupiáñez, 2010). Low trait BIS can lead to externalizing disorders (Bijttebier, Beck, Claes, & Vandereycken, 2009), in that the inhibition effects of BIS are low. People high in BIS reactivity are risk averse, and extreme BIS can lead to anxiety, often diagnosed as generalized anxiety disorder (Corr, 2008; McNaughton & Corr, 2004).
**Constraint (EF)**

The RST systems explanation, as hypothesized by Gray and McNaughton (2000), is that all RST systems are self-regulatory, in that top-down prefrontal processes aid in approach and avoidance, as a part of BIS and BAS systems. BAS was believed to take care of approach through sub-goal scaffolding (Corr, 2008). Here, the first step is identifying the biological reinforcer, the second is planning behavior, and lastly there is execution of plan (Corr, 2008). So the BAS is supposed to pertain to the whole complexity of the process of goal acquisition. The RST model, however, does not adequately state how this would happen. In basic RST theory BIS is conceptualized as the regulatory system of the BAS, in that it stops ongoing behavior, if necessary (Corr, 2008). An argument against the BIS being the only RST regulatory system, is that while anxiety is the emotional outcome of the BIS (Gray & McNaughton, 2000) there is reason to believe that not all regulatory processes are associated with anxiety (Carver, 2005).

The definition of neural systems will be repeated here, as structures that interlink, and serve a common functional purpose (Woolsey, 2019). A focus from cognitive psychology may be worth integrating into RST theory. Miyake et al. (2000) defined executive functioning (EF) as “general-purpose control mechanisms that modulate the operation of various cognitive subprocesses and thereby regulate the dynamics of human cognition” (p. 50). EF may be a neural system, with superordinate cognitive power over other neural systems and processes. There is also reason to incorporate the cognitive executive functions in the study of psychopathology and self-regulation, as there is limited but increased evidence of the involvement of cognitive control in adaptive behavior (Hofmann, Schmeichel, & Baddeley, 2012).

Carver (2005) provided an analysis of the RST and other personality models, suggesting *constraint* to be the common personality factor that is missing in RST conceptualization. Krupić and Corr (2017), discussing the RST, wrote that most behaviors have simple subgoals, to the extent of the process being reflexive. However, Kennis et al. (2013) proposed constraint to be a regulatory system that can inhibit or override the other three systems, and also account for volition and effortful control. This should involve at least some conscious control and thinking awareness, and thus more reflective processes. Constraint (EF) as a fourth RST factor is believed to be superordinate to FFFS, BIS and BAS, and through this provides a regulatory system of emotion and behavior (Kennis et al., 2013). EF is hypothesized to act upon the highest levels of the other RST systems, and when stimulus bottom-up intensity is low (Kennis et al., 2013). A full analysis of constraint as a
concept cannot be provided here. However, in this paper a four-factor RST model which includes a separate system of top-down cognitive control is supported.

Below is a description of symptoms in a 10-year old girl. Several directional hypotheses may be stated from this description. Symptoms may be due to inefficient top-down regulatory processes, excessive bottom-up signaling, or a maladaptive interplay between systems.

She is easily distractible, has excessive and constant motor movement. Parental regulation has been difficult from early age.

(Par

ent in clinical interview, girl aged 10, oppositional disorder, attention deficit disorder and subclinical DMMD due to non-presence of symptoms at school)

An explanation to this symptomatology may be found from research using integrative models, such as the RST. The foundation of the RST is neuroscientific, and an illustrative model of the RST and its neural constituents is provided at this point in Figure 1. This oversight is provided here, due to neural explications being used in further analysis. The BIS, BAS, FFFS and EF/ constraint systems are described in terms of hypothesized central neural structure involvement.

**Figure 1**

*RST Neural components, systems interaction and behavioral outcome*

---

**Abbreviations:** FFFS; fight, flight, freeze system, BAS; behavioral approach system, BIS; behavioral inhibition system, PFC; prefrontal cortex, ACC; anterior cingulate cortex, mHypothalamus; medial hypothalamus, PAG;
periaqueductal grey, PCC; posterior cingulate cortex, SHS; septohippocampal system, and VTA; ventral tegmental area.

Figure 1 is adapted from Kennis et al., 2013.

**Theoretical Subsystems Interaction on a Trait Level**

One important question in RST research is how systems interact on a trait level. There are two opposing hypotheses regarding systems interaction. The *separable subsystems hypothesis* (SSH) states that the BIS/ (FFS) and BAS are independently functioning systems (Corr, 2004). This means that in personality functioning one level of BIS sensitivity is independent of the BAS, such that individual predisposition towards reward (BAS sensitivity) is independent of BIS predisposition, and vice versa (Corr, 2002). The *joint subsystems hypothesis* (JSH) opposes the SSH, stating that BIS and BAS, being related to anxiety and extraversion/imulsivity, respectively, act in a dependent fashion (Corr, 2002). According to the JSH, the level of one system correlates negatively with the level of the other.

**The Usefulness of RST in the Conceptualization of Psychopathology**

**Internalizing Disorders**

The most consistent and thorough research in the RST tradition has been on BIS as a marker for anxiety (Corr, 2008). Both generalized anxiety disorder (GAD) and obsessive compulsive disorder (OCD) are believed to be related to BIS activation (Gray & McNaughton, 2000), however with cognitive aspects of GAD being controlled by the septo-hippocampal system, and OCD risk assessment being located primarily in the connections between the cingulate and basal ganglia. Anxiety and depression are both related to BIS activation (Vervoort et al., 2010), however low BAS in the form of anhedonic depressive symptoms may exacerbate the effect of BIS on psychopathology (Hundt et al., 2007).

**Externalizing Disorders**

Externalizing disorders have been found to be related to either low BIS or high BAS reactivity (Corr, 2008). Quay (1988; 1993; in Carver and White, 1994) found that conduct disorder (CD) was related to hyperactive BAS, while children with ADHD had a low BIS. In more contemporary pharmaco-behavioral research, Corominas et al. (2013) found ADHD and externalizing aggressive behavior to be related to blunted cortisol levels, while increased cortisol response was related to comorbid anxiety. They concluded with the hypothesis that severe cases of ADHD may have low cortisol production, associated with an underactive BIS. Bijttebier et al. (2009) also reviewed a study that linked strong BAS to ADHD.

**Combined Type**

There is some evidence for the joint presentation of hyperactive BIS and BAS (BIS+)
BAS+) in clinical and low-functioning samples, and in line with the SSH presented above. The existence of BIS+/ BAS+ is rare (Windle, 1994), as studied in a large US military sample. However, when both were present, people showed a mixture of internalizing and externalizing lifetime psychiatric disorders, as well as increased symptom load. Soler et al. (2014), studying individuals diagnosed with borderline personality disorder (BPD), found that many with this diagnosis had the combination of BIS+/ BAS+. A question regarding DMDD is whether these children have a combined neural sensitivity, with hypersensitive BIS and BAS, in line with the SSH. There are also possible effects of FFFS and EF upon DMDD presentation that needs further evaluation.

**RDOC Overlap and Limitations**

This section started with an outline of the RDoC in Table 1, and an argument that RDoC and RST have significant conceptual overlap. Table 2 provided oversight over RST dimensions, emotions and correlates. Table 3 below outlines DMDD DSM-5 symptoms and hypothesized overlap with RDoC constructs and RST dimensions. The next section will look at DMDD and other disorders that may overlap with DMDD presentation.

**Table 3**

*APA DMDD Criteria, Research Domain Criteria and Reinforcement Sensitivity Theory of Personality Dimensions*

<table>
<thead>
<tr>
<th>DSM-5</th>
<th>RDoC</th>
<th>RST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temper outbursts</td>
<td>Approach motivation</td>
<td>BAS, drive, EF</td>
</tr>
<tr>
<td>Verbal</td>
<td>Reward learning (RPE)</td>
<td>BAS</td>
</tr>
<tr>
<td>Behavioral</td>
<td>Initial/ sustained responsiveness</td>
<td>BAS, reward sensitivity</td>
</tr>
<tr>
<td>Arousal</td>
<td>Acute threat</td>
<td>FFFS</td>
</tr>
<tr>
<td></td>
<td>Frustrative nonreward</td>
<td>FFFS/ BIS</td>
</tr>
<tr>
<td></td>
<td>Social communication</td>
<td>FFFS?</td>
</tr>
<tr>
<td>Mood irritable or angry</td>
<td>Sustained threat</td>
<td>BIS/ (FFFS)</td>
</tr>
<tr>
<td></td>
<td>Potential threat</td>
<td>BIS</td>
</tr>
<tr>
<td>Not in clinical</td>
<td>Attention</td>
<td>EF, or part of BIS/ BAS?</td>
</tr>
<tr>
<td>definition</td>
<td>Visual vs verbal WM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EF</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* “Drive” and “reward sensitivity” are dimensions of BAS, derived from self-report measures (e.g. Carver & White, 1994). *Abbreviations:* RPE; Reward prediction error. WM; Working memory. FFFS; fight, flight, freeze system. BAS; behavioral approach system. BIS; behavioral inhibition system. EF; executive function.
Attempting to Single out DMDD in Differential Diagnostics

A question outlined in this paper is how DMDD neural and behavioral features may be different to other childhood disorders. Irritability being a feature of childhood disorders on the internalizing-externalizing spectrum (APA, 2013), makes irritability as a phenomenon relevant cross-diagnostically. Presented irritability may have different etiologies. In this section DMDD will be compared to bipolar disorder, attention deficit hyperactivity disorder (ADHD), ODD, depression and anxiety. In line with the third research question, this comparative effort will start to outline a DMDD neural and cognitive profile.

DMDD is not Bipolar Disorder

In the years of 2003-2013, childhood persistent irritability was understood as a phenotype of bipolar disorder (BD). Leibenluft, Charney, Towbin, Bhangoo, Pine (2003) proposed severe mood dysregulation (SMD) as the clinical term for this non-episodic irritability. Angry or sad mood, hyperarousal, a high level of reactivity to negative emotional stimuli, as well as rage outbursts, were proposed to be the critical features of the clinical picture of these children (Leibenluft et al., 2003). However, the administration of mood stabilizers was found unsuccessful for patients receiving the diagnosis of SMD (Masi & Gignac, 2016), and long-term outcome for bipolar narrow type and broad phenotype (SMD) differed (Brotman et al., 2006). Different etiologies could be assumed for BD and SMD.

Children with irritability and anger outbursts have difficulty inhibiting maladaptive behavior. Stop-signal tasks are part of paradigms that require inhibition of prepotent response. Deveney et al. (2012), using this paradigm, compared behavioral and neural response in children and youth with SMD, BD, ADHD and healthy controls (HCs). They found no difference in reaction times and accuracies between groups. However, fMRI imaging presented evidence that BD and SMD are distinct conditions, with neural response in the ACC and the right nucleus accumbens being smaller in the BD group when failing the task. The neural response in these regions was the same in SMD and HC, signifying possible adaptively functioning motor inhibition in SMD subjects. The stop-signal task usually being able to distinguish behaviorally between impulsive and normal populations (Aron & Poldrack, 2005), suggests that SMD impulsivity can possibly not be explained in terms of stop-signal deficiency.

Behavioral and neural response may be more affected in children with DMDD when presented with emotionally salient stimuli. Rich et al. (2007; 2011) induced negative affectivity in BD, SMD and HC, using an affective Posner task. This task included a condition
with rigged feedback. In the rigged feedback condition, participants were told that they responded incorrectly or that they were too slow in responding on a percentage of trials, even if they had made the right choice. The SMD group consistently reported higher arousal (Rich et al., 2007; Rich et al., 2011) and being less happy (Rich et al., 2011) than the comparison groups during these frustration tasks. Psychophysiological recordings were related to SMD impairment in initial stages of attention, and BD executive functioning difficulties (Rich et al., 2007). Magnetoencephalography provided evidence that neural response upon rigged feedback in the SMD group was related to increased ACC and medial frontal gyrus (MFG) activation (Rich et al., 2011).

The general findings here were that BD and SMD present neurologically differently to stop-signal tasks and to frustration paradigms. Children with SMD also reported lowered mood and heightened arousal compared to children with BD. Behaviorally, however, there seems to be adjusted performance, so that neural activation did not reflect in actual performance on task. The exception was the Rich et al. (2007) study, where BDs were slower than SMDs that were slower than HCs on the rigged frustration task.

**DMDD and ADHD**

The DMDD category does not have diagnostic overlap with ADHD with symptoms of hyperarousal and distractibility, such as SMD did. However, DMDD frequently presenting together with ADHD (Mayes et al., 2015), necessitates assessing shared and separate contributions to behavior and psychological functioning. This work is only just beginning. Taskiran, Mutluer and Necef (2017) compared participants with ADHD, DMDD with comorbid ADHD and healthy controls on a wide range of neuropsychological tests requiring executive functioning. There were non-significant differences between clinical groups on all EF tests, except for children with DMDD being significantly slower on the Trail-Making Test, a test of processing speed and divided attention. However, there was slightly lowered performance on all tests for participants with DMDD and comorbid ADHD, suggesting the existence of additional cognitive control difficulties with DMDD/ADHD comorbidity issues. This study paves the way for further studies on the nature of executive functioning difficulties in children with DMDD. However, this study did not provide a “pure” DMDD group, so that possible executive function difficulties specific to the DMDD group could not be examined.

In a recent neuroimaging study using a selective attention task with groups of ADHD, DMDD with attention problems, and HCs, Pagliaccio et al. (2017) found that both clinical conditions showed a deficit in sustained attention. For DMDD there was heightened pre-stimulus activity before long reaction time trials in several neural regions, suggesting a
separate pathology of DMDD. This may signify that children with DMDD have heightened processing, rather than lowered. However, this processing did not improve task performance, and may thus be task-irrelevant. It was also found that it was degree of severity of irritability in the DMDD/ADHD group that was a significant factor, in that it correlated with longer reaction times.

One study, examining a pure DMDD group comparatively, in the above-mentioned affective Posner paradigm, was by Tseng et al. (2015). Behavioral results were not reported, however researchers suggested that DMDD has different neural reactivity to ADHD, anxiety as well as healthy controls, specifically represented in the parahippocampal and the superior temporal gyri. The researchers wrote that these regions are implicated in emotion regulation and social perception, and are assumed to mediate irritability in general in youth.

**DMDD = Oppositional Defiant Disorder (ODD)?**

While APA (2013) conceptualizes DMDD as a mood disorder, the World Health Organization classifies severe irritability as a sub-category of ODD (WHO, 2018). The APA (2013), acknowledging DMDD comorbidity with ODD, stated that only about 15% of children with ODD would also have comorbid DMDD, in which case diagnosing DMDD would take precedence over ODD. Differentiating between DMDD and ODD may be challenging. Mayes et al. (2015) suggested that with parent report, ODD and DMDD could in fact not be differentiated. Runions, Stewart, Moore, Ladino and Rao (2016) underlined the necessity of diagnostic scrutiny. They pointed to the fact that ODD is understood as a combined non-compliance/irritability disorder. These are co-occurring, but distinct features in clinical presentation, and need to be assessed separately.

While there are as of yet no comparative studies on neural and behavioral correlates of ODD and DMDD, Evans et al. (2017) wrote the article leading up to the WHO definition of childhood irritability (WHO, 2018). One of their concerns about formulating the DMDD diagnostic category was that most research prior to the formulation of the diagnosis was on severe mood dysregulation. They also reviewed studies that had found that the vast majority of DMDD-related symptomatology had prevalent comorbid ODD symptoms. Stringaris and Goodman (2009), however, believed that ODD consists of the separate dimensions of irritability, defiance and hurtfulness. Defiance and hurtfulness, or callous traits, as seen in antisocial behavior, may be needed to be singled out as non-DMDD features if one would meaningfully divide between DMDD and ODD. The low physiological reactivity and low processing of distractor stimuli, as found in individuals with anti-social traits (Wallace & Newman, in Corr, 2008), may be a feature specifically related to oppositionality and low BIS,
rather than irritability, *per se*.

**DMDD as a Depressive or Anxious Disorder?**

_Hostile attribution bias* (HAB) is the propensity to interpret ambiguous information negatively, leading to depressive thinking and interpersonal difficulties (Gadassi & Rafaeli, 2015). Banks, Scott and Weems (2018) also found that hostile attributions could lead to elevated levels of anxiety, measured in heart response. While it is inconclusive whether children with DMDD have a HAB tendency (Brotman et al., 2017), in children with SMD, an attention bias towards angry faces has been found (Hommer et al., 2014). In a study where children with SMD rated own fear when presented with face stimuli, amygdaloid hypoactivation was observed, assumed here to be relatable to the depressive aspects of SMD (Brotman et al., 2010). While there is differential neural activation in DMDD from anxiety disorder during frustration induction (Tseng et al., 2015), suggesting they have different etiologies, DMDD has been found to be related to anxiety both as a comorbid disorder (Copeland et al., 2013) and longitudinally (Copeland et al., 2014; Stringaris, Cohen, Pine, & Leibenluft, 2009). These results may signify that there is some overlap in terms of neural composition of sensitivities with anxiety and depression. However, DMDD presentation is different from the anxious-depression spectrum in that it has externalizing features in more severe and frequent anger outbursts, either verbally, physically or both (APA, 2013).

**Section Summary**

In the preceding section studies attempting to differentiate DMDD from other clinical presentations were presented. The first differential diagnostic studies distinguished between BD and SMD. Differences were found in activations of the nucleus accumbens (Deveney et al., 2012), the ACC and the MFG (Rich et al., 2011), and Rich et al. (2007) suggested that SMD pathology was related to initial impairment of attention. The studies that reported on behavior on ADHD and DMDD did not separate a DMDD group without attention difficulties (Pagliaccio et al., 2017; Taskiran et al., 2017), so there is still no clarity as to whether there exists a DMDD without attention difficulties, and whether they present with difficulties that are not related to ADHD symptomatology. A comorbidity effect, where DMDD/ ADHD scored a bit lower on a range of EF tests, and significantly different on a test requiring visual dual attention, was however found (Taskiran et al., 2017). ODD has oppositionality as a central feature, while irritability is linked with internalizing disorders long-term. The callous-unemotional trait is assumed to be the feature that functionally separates between ODD and DMDD. The similarities to depressive and anxiety disorders have been explored, in that studies have found a possible common bias toward threat. In sum, there is reason to
distinguish DMDD from ODD and from BD, however the above analysis points to a hypothesis that attention difficulties and depressive and anxious aspects may be a part of the DMDD clinical presentation.

**Further Delineating DMDD in Terms of RST/ RDoC Constructs**

The third and most central question in this paper is whether one can use the RST dimensions and parts of the RDoC in order to understand DMDD pathological processes. The above section delineated DMDD as a disorder with some differences in neural activation from BD, as well as possibly from ODD and ADHD, and with neural threat activation such as that seen in depression and anxiety. In this section a start of an RST theoretical understanding of DMDD, will be provided. The first question to be addressed here is anger from a neural perspective. Threat processing will also be given special attention. A possible learning deficit, with underlying deficient BAS signaling will also be presented. Finally, the dominant hypotheses in the field with regards to the etiology of DMDD will be presented.

**Anger**

One of the diagnostic criteria for DMDD is having frequent and severe anger outbursts disproportionate to the situation and normative expectations of behavior for the child’s age (APA, 2013). Carver and Harmon-Jones (2009) presented evidence that anger is related to BAS-activation. Harmon-Jones (2003) found that physical aggression in particular was related to BAS hyperactivity. An interpretation with regards to these results is that aggression may involve movement towards a goal, which is BAS-mediated. An alternative perspective has also been presented. Muris et al. (2005) found that low BIS was related to symptoms of hyperactivity, conduct problems and aggression in a sample of primary school children. This suggests a disinhibition effect that may lead to increased anger expression. There seems to be multi-faceted causality into the expression of anger.

In line with the discussion above regarding ODD, there may be a need to distinguish between reactive and proactive aggression in the understanding of DMDD. Some aggressive behaviors are results of callous-unemotional traits. These are linked to low levels of empathy and guilt, and disregard for others (Frick & Morris, 2004, in Waller et al., 2016). While antisocial personality disorder is rare, behavioral disorder in childhood predisposes for antisocial behavior in adulthood (Biederman et al., 2008). In RST terms, antisocial and impulsive behavior is a form of disinhibition. There may be reason to distinguish between irritability as an internalizing feature, and oppositionality as an externalizing feature. If one is to evaluate the nature of anger in children with DMDD, one needs to be aware of the
mechanisms triggering the anger. While ODD/CD may be a BIS-/BAS+ combination, DMDD is likely a BIS+/BAS+ version. The disruptive behavioral disorders may have more instances of intentionally hurting others, for example, as opposed to DMDD.

Blair (2012) reviewed anger from a neuroscientific perspective, and found reactive anger to be related to activation of the basic threat system. While the RST is not mentioned in this article, Blair referred to the Gray and McNaughton (2000) FFFS neural structures. Blair (2012) used the examples of post-traumatic stress disorder (PTSD) and borderline personality disorder (BPD) to underline what happens to individuals in threatening environments. He found amygdaloid hyperresponsivity to be the common neural feature of these disorders. This means that upon increased exposure to threat, FFFS is sensitized and increasingly responsive, and people also become more anger prone (Blair, 2012) as a part of the fight-fight-freeze conglomerate of threat responding.

One question arising from Blair’s (2012) analysis with regards to DMDD, together with Carver and Jones’ (2009) analysis, is whether anger shown by people diagnosed with DMDD is instrumental or BAS-approach related, or alternatively, if it is more fear/threat-related. As hypothesized in the RST, there are two forms of anger. One is a FFFS-response, seen as a direct response to close threat (Gray & McNaughton, 2000). The other is BAS-related, as discussed by Carver and Harmon-Jones (2003; 2009). One may assume that there to be more conscious representation, or a time lag in responses in more BAS-related aggression, with evaluation of outcome, and possibly a more proactive feature.

If DMDD childhood temper outburst neural presentation fit with Blair’s theoretical presentation, a hypothesis to deduce from this is that children with DMDD have hyperreactive FFFS alarm systems. Children with DMDD, while not necessarily having been subjected to threatening environments, may still have this reactivity as an inborn capacity. It is also likely that early difficult temperament presentation may lead to parent and other significant adult and peer anger responses, so the FFFS is constantly sensitized through interaction. Deveney et al. (2013) found hypoactivity of the amygdala in response to frustration in severely irritable children (SMD), not in line with the hypothesis that children with DMDD have a hyperactive BIS/FFFS. However, the fact that there are substantial comorbidity issues in the clinical diagnostic (Mayes et al., 2015), the Deveney et al. (2013) results may possibly have been confounded by an ODD comorbidity. The ODD hypoactivity of the amygdala to negative stimuli, is in line with the results of Knafo, Jaffee, Matthys, Vanderschuren and Schutter (2013), finding ODD low punishment sensitivity to be one cause in their inefficient processing and behavioral difficulties.
Amygdaloid hyporesponsivity found in irritable children (Brotman et al., 2010; Deveney et al., 2013) suggests a neural dysfunction. This hypoactivation is not in line with heightened threat detection. However, it may be that neural activation and behavioral response are already executed at lower neural levels, in the FFFS PAG or medial hypothalamus. Also, Vidal-Ribas et al. (2016) found amygdaloid hyperactivation in irritable children upon implicit processing, suggesting a higher activation when activation is direct and unfiltered. DMDD anger is possibly both related to a FFFS alarm-mediated anger at instant levels of threat, and with BAS more premeditated behavior at more distant levels.

**Possible BIS Engagement in Irritability and Anger**

While possible BAS and FFFS engagement in anger expression have been examined above, there is also reason to research the separate contribution of the BIS. Longitudinal DMDD outcome in anxiety and depression (Copeland et al., 2014), is conducive to thinking that children with DMDD have hyperactive BIS systems. In a study with adults, Smits and Kuppens (2005), found that BIS was more related to inward expression of anger, as opposed to BAS. This means that anxiously prone or BIS sensitive people are less likely to exhibit anger. This does not fit with the clinical picture of children with DMDD, who do show anger.

The BIS is typically seen as underlying withdrawal and anxiety (Corr, 2008). However, factor analytic research has given evidence towards anxiety and threat avoidance loading together with anger and irritability (Watson et al., 1999, in Carver & Harmon-Jones, 2009). This might indicate that anger arises from neural processes that are BIS-related. In a study with university volunteers, Harmon-Jones (2003) found that trait anger, trait hostility, BIS and *general negative affect* were factors that correlated. It may be that negative affectivity and hostility-proneness is the inter-outburst mental state of children with DMDD. The link to findings on children with DMDD having a hostile attribution bias (Stoddard et al., 2016), also suggests that there may be negative thoughts between outbursts. So BIS as a whole may not elicit anger, but ruminational thinking might. The separation of two BIS-related constructs, *anxiety* and *rumination*, may be meaningful when describing children with DMDD. There is not enough understanding of the patterns of the thinking of children with DMDD and whether or not anxious rumination can be directly linked to anger outbursts. There is also insufficient evidence with regards to top-down inhibitory control processes. Certainly, the following excerpt from a clinical interview with this boy’s parents shows in his case BIS and BAS reactivity, BIS subsisting of the depressive and anxious symptomatology.

The boy has daily outbursts of crying and despair. He worries a lot, and seems ruminative. He also has problems falling asleep. He is in and out of this mood
expression during the day. He also fights with parents, often when they want
him to do things and they repeat the message until they give the message in an
angry voice.

(Parents in clinical interview, boy aged 8, diagnosed with DMDD)

There is some support to the presumed ruminational nature of children with DMDD. Pagliaccio et al. (2017) found increased neural activity in selected regions preceding lowered performance on task for children with DMDD with attentional difficulties. This activity separated them from children with ADHD and HC. In the Rich et al., (2007; 2011) studies, children with SMD reported more arousal, and initial impairment of attention was the result. Perlman et al. (2015) showed increased PCC activation when faced with non-reward. The PCC activation may be related to the emotionality of irritable children. In frustration paradigms, it may be that the BIS activates to a greater degree in children with irritability. PCC being BIS related (Kennis et al., 2013), DMDD BIS sensitive may have excessive internal mentation upon frustration, deactivating BAS which is also related to active and functional problem-solving (Corr, 2008). Indeed, Taubitz, Pedersen and Larson (2015) found that a facet of BAS, reward responsiveness, predicted adaptive functioning. So it may be that it is partially BIS reactivity that undermines adaptive behaviors in children with DMDD, and induces angry behaviors.

Children with DMDD May Have Learning Deficits

One dimension of the RDoC, the positive valence systems, treats aspects of reward (Cuthbert & Insel, 2013). Reward responsiveness is an RST BAS (Carver & White, 1994), as well as an RDoC construct (NIMH, 2019). Kessel et al. (2016), through the use of EEG with a sample from a prospective study on temperament and risk for psychopathology, screened and found 373 children that fulfilled DMDD criteria at age three. At age nine they were presented with a monetary reward task. The main finding in this study was that children with DMDD symptoms at age three and of male gender, exhibited increased RewP when presented with monetary rewards at age nine (Kessel et al., 2016). This is an EEG response positivity to rewards, associated with striatal and medial PFC activation. Blunted responsiveness was related to ODD symptomatology, further underlining that ODD and DMDD have different etiologies. DMDD did not predict N200 measurement, a negative EEG response to loss. Predictions here were specific to reward. This neural sensitivity found by Kessel et al. (2016), may be the neural constituents of reward responsiveness, an RDoC and RST BAS-related concept, which means that children with DMDD may have an increased sensitivity to reward.

There are also results on specific sensitivity to loss for children with DMDD. Reward
prediction error (RPE) is an RDoC positive valence dimension (NIMH, 2019), and relevant with regards to BAS functioning. It is defined as “the difference between expected and received reward” (Schultz, 2016, in Meyers et al., 2017), and is mirrored in neural signaling. When a reward is received or when a stimulus connected to a previous reward is shown, activity in midbrain efferent neurons increase (Meyers et al., 2017). Normative response upon loss is that dopaminergic midbrain projections decrease signaling to striatum (Abler, Walter & Erk, 2005; Schultz, 2002). Adleman et al. (2011), in a reversal paradigm where change in conditions signals a loss, showed that clinical groups failed to decrease signaling of change in the caudate (BD and SMD groups) and inferior frontal gyrus (IFG). The IFG failure was specific to the SMD group, also mirrored in more errors on the reversal task. It seems that learning is compromised here due to reduced flexibility and deficiency in signaling. A relevant reservation to these results was that the failure of the caudate nucleus to reduce its signaling in the event of error may have been due to ADHD comorbidity.

Heightened reward sensitivity (Kessel et al., 2016), as well as decreased signaling when contingency changes (Adleman et al., 2011), may be part of the neural explanation for irritability. This cognitive malfunction may have widespread effects in everyday life. If a child’s brain is wired for certain expectations, that are frequently not being met, there is certainly ground for mood changes in negative direction. A behavioral rigidity and countermeasure strategies may be implemented by these children as a means to counter this neural deficiency. The BAS is involved in impulsivity, and Kessel et al. (2016) observed a heightened response to rewards. This may result in more impulsive behavior. BAS system failure, as shown by Adleman et al. (2011), failing to detect change though caudate activation, may set off a signal to the BIS. This may happen to a greater degree in children with DMDD, and may be a precursor to a state of negative affect (Eisenberger et al., 2005).

**Frustrative Nonreward**

Frustrative nonreward is a separate field of research proposed by the RDoC (Insel & Cuthbert, 2013). Amsel (1958, in Brotman et al., 2017) studying rodents, defined frustrative nonreward (FNR) as an adaptive response. It is an emotional and behavioral response to blocking of expected rewards, and involves increased motor activity in all species (Brotman et al., 2017). FNR is an instinctual and immediate behavior. This means that the expression of the frustrative nonreward is not always in line with human societal norms. If an individual has increased propensity for maladaptive reward processing, as demonstrated in the above analysis of the reward prediction error, there is also likelihood for increased frustration.

While striatal activity decreases upon nonreward in normal populations, there are also
egocentric effects (Abler et al., 2005). Hypothesized to underlie this emotional egocentric effect, the anterior insular cortex, the ACC and the right ventral PFC activated when there was omission of reward. These regions, being linked to pain activation, were in this case hypothesized to be linked to emotional pain. One may also conceptualize this activity as a type of error signaling (BIS), where the ACC and anterior insula opens up for FFFS activation, in case of needed escape. In error detection, the ACC is activated (Gehring & Fenszik, 2001, in Margulies et al., 2007), and signals of nonreward are likely computed as a detected error. Arousal and readiness may be the neural response. Of interest, there is a frustration effect of FNR, leading to e.g. faster running after FNR induction (Ryan & Watson, 1968). So upon error or nonreward it seems that neural processing heightens sympathetic outflow.

There is some evidence that the DMDD diagnosis entails increased reactions to FNR. Upon frustration, youths with clinical irritability show neural dysfunction in the PFC, the ACC, striatum, amygdala and the PCC (Deveney et al., 2013; Grabell et al., 2018; Perlman et al., 2015). These neural activations may be linked to all RST systems. Increased error detection/ FNR responses likely involves the BIS, and top-down EF processes should have a role in adaptive regulation of emotion and behavior. The deficient activation pattern cited here leads to thinking that it may be reasonable to conceptualize DMDD in terms of an RST systems interaction. An emotional and behavioral response to nonreward should involve neural involvement from all dimensions of the RST model.

The Two Neural Explanations of DMDD

Brotman et al. (2017) and Leibenluft (2017) summarized the current knowledge about childhood irritability. There seems to be agreement that a dual systems failure is underlying DMDD. Firstly, as shown above, children exhibiting irritability show increased frustration upon absence or delay of reward. Diminished signaling of the reward prediction error or a BAS system dysfunction may underlie the difficulty. Secondly, there may be an FFFS-related difficulty. Brotman et al. (2017) summarized possible aberrant threat responses from three behavioral-neural paradigms. First, children with DMDD seem to be attentionally probed towards threat (Hommer et al., 2014), so that presenting angry faces as stimuli will require excessive cognitive resources. Furthermore, hostile attribution bias (HAB) has been related to anger and aggression, but here there is still limited and conflicting evidence on the DMDD group with regards to the presence of a HAB (Brotman et al., 2017). In addition, irritable children have an increased tendency to see threat in neutral faces. Being central RST and RDoC concepts, aberrant threat and reward processing seems to be a central feature of
children with DMDD. The hypotheses of these researchers are consistent with the research reviewed in this paper.

**Section Summary**

In the preceding section the concept of *anger* was explored. A distinction between reactive and proactive anger has been made, in terms of trying to distinguish between childhood irritability and oppositionality. BAS was presented as underlying aggressive movement. FFFS was positioned in the understanding of anger, as a threat response due to the specific neural sensitivities of children with DMDD. FFFS-mediated aggression was proposed as the dominant form in children with DMDD. Furthermore, rumination or negative affectivity, have been proposed as BIS contributions to anger. *Reward prediction error* and *frustrative nonreward* are RDoC constructs in which children with DMDD have shown aberrant processing. The most recent DMDD hypothesis is one of aberrant threat and reward processing (Brotman et al., 2017; Leibenluft, 2017). These results line up with RST thinking. For now, the hypothesis is that children with DMDD have hypersensitive FFFS, BIS and BAS. In the next section these propositions will be treated further.

**How to Understand DMDD Using RST Dimensions**

Evaluation of the usefulness of the RST as a model for understanding DMDD is an important focus in this paper. Here, an extension and consolidation of selected RDoCs and the RST will be made, together with suggestions for future research. As highlighted in the previous section, the dominant hypotheses for children with DMDD are that they have aberrant responses to frustration and threat, as well as deficiencies in reward learning (Brotman et al., 2017; Leibenluft, 2017). In RST terms, the working hypothesis becomes that children with DMDD have hyperactive responsivities in FFFS (threat/alarm signaling), BIS (ruminational tendency) and BAS (impulsivity). This may be coupled to certain difficulties with executive functioning, as seen in the previous section on differential diagnostics. The question of EF involvement will be treated further here, together with hypotheses of timeline responsivities of systems. Model-wise and simplified, FFFS+, BIS+, BAS+ and EF-, is the suggested combination for system engagement in children with DMDD. The central role of the anterior cingulate cortex in systems interaction will be professed. The bottom-up systems may have separate and mutually reinforcing sensitivities. For EF, increased emotional and behavioral reactive systems may be compromising the efficiency of top-down control. Suggestions for testing of separate functional involvement of systems will be forwarded, starting with the FFFS.
Testing Hypothesized Neural FFFS Sensitivity

Due to the focus here on FFFS involvement, there may be reason to test FFFS on a basic level. LeDoux (2015) pointed out that there is an essential distinction between the non-conscious defense system, elicited by threat, and the processes that lead to the conscious feelings of fear. In this paper the initial alarm defensive system has been a focus, rather than the conscious processing of fear. In most FFFS signaling one may propose that people are not fearful, rather that the FFFS constitutes an alarm signal that does not reach conscious processing levels. To test the FFFS alarm hypothesis, there may be some merit in testing neural reactivity in a basic way.

Corr and McNaughton (2008), suggested punishments of all kinds to be relevant for testing FFFS reactivity. Another possibility may be testing early childhood startle responses. A startle to an abrupt stimulus may be seen as a behavioral output of the neural sensitivity of an alarm system. This makes the startle conceptually a behavioral response supported by the FFFS system. However, the startle reflex is modulated by different neural inputs (Blanch, Aluja, Blanco & Balada, 2016). Therefore, early infancy testing of the startle may be necessary if one is to assume that startle sensitivity can predict childhood irritability. Abend (2018) found that early fearful temperament measured on a scale predicted the development of anxiety in preadolescence. Whether the hypothesis of FFFS sensitivity as an initial temperament/vulnerability holds up must be tested in such longitudinal designs.

A threat bias towards angry faces has also been measured in children with DMDD (Salum et al., 2017). This may be seen as a social processing deficit that essentially is a threat signal to the FFFS, alternatively as an effect of a hyperactive FFFS. Leibenluft (2017) proposed using fMRI paradigms of more ecological validity to examine threat reactivity in children with DMDD, such as social computer games where individuals believe they play with another person, where the other player steals from the participant. Other options would be social stories, wherein children with DMDD are asked to attribute the intentions of others. There are various ways in which to study whether children with DMDD attribute hostile intentions to others and whether they interpret ambiguous situations as threatening, with and without neural imaging. fMRI studies with a specific focus on RST systems involvement in social situations may aid in understanding whether children with DMDD process various situations as threatening.
Trying to Elucidate Neural Aspects of Frustration

_Frustration May Elicit the FFFS_

As children with DMDD are assumed to experience substantial frustration, the understanding of the neural underpinnings of this frustration is essential. A tentative RST explanation will be provided here. One of the hypotheses regarding DMDD is that neural dysfunction in the striatal reward system gives rise to heightened FNR response (Brotman et al., 2017). Diminished RPE is relevant for DMDD. It has been found with the SMD group (Adleman et al., 2011) that neural reward processing efferent signals to the cortex is lessened upon nonreward, compared to non-irritable children. While studies on childhood irritability response to frustration have reported and focused on striatal and cortical structures (Perlman et al., 2015; Rich; 2011, Tseng et al., 2019), Abler et al. (2005) also underlined what they called the egocentric effects of frustration. The right anterior insula and the right ventral PFC were active upon omission of reward. According to Kennis et al. (2013), the ventral PFC is a FFFS neural mediator, so this nonreward related neural activation may be linked to it being processed as a threat. Abler et al. (2005) assumed this activation to be related to emotional pain as the nervous system detects error. If one assumes that pain signaling is an intrinsic threat stimulus, one may also claim that FNR activates the FFFS.

_Frustration May Elicit Fear, Which May Elicit Inhibition_

Leibenluft (2017), citing Gray (1987), suggested that frustration is processed like fear, with stimuli discordance being a threat signal. In line with theory, Gray also suggested BIS to be a mediator in frustration, when threat and reward appear simultaneously like in the RPE paradigm (Leibenluft, 2017). Yu, Mobbs, Seymour, Rowe and Calder (2014) studied escalation of frustration in a healthy sample of 27 male volunteers. During an escalating frustration win-blocking-loss task due to manipulated proximity to, and amount of effort used to obtain reward, the amygdala, the periaqueductal grey (PAG), the insula and the dACC were increasingly involved. This is a system related to rage in rodents (Yu et al., 2014), which may be assumed to underlie the fight response made possible through the FFFS.

There is very little knowledge on the systems interaction between the FFFS and the BIS. McNaughton and Corr (2004) suggested FFFS and BIS to be represented at all levels of the same neural structures in a parallel fashion. Due to Yu et al. (2014) alternating between win and loss, the BIS is theoretically intrinsic to this task (Gray & McNaughton, 2000). Interestingly, with increased effort and frustration, more right-sided structure activations were registered (Yu et al., 2014), possibly mirroring regulation efforts. This observation of structural left and right side co-activation with intensified level of effort due to increased
frustration may be related to BIS system inhibition upon the FFFS. Carver and Harmon-Jones’ (2009) analysis of BIS activation, was also that BIS activated more right-sided structures.

The Yu et al. (2014) results are in line with the thinking of Gray (1991) that systems inhibition happens in feedback loops, however the BIS is believed to inhibit the BAS, not the FFFS (Corr, 2008). Yu et al. (2014) believed the added activation observed resulted in increased behavior invigoration effects. While this belief is not in line with there being inhibition, there may also be simultaneous effects, both withholding and preparing for behavior. This study is of special interest with regards to children with DMDD, due to their proclivity for frustration. While it resembles the Posner paradigm previously reported here, this study includes gradation of motivation and frustration, which may have specific effects on performance in children with DMDD. Using a similar design may also be useful in delineating the specific involvement of the BIS and the FFFS, and possibly also top-down control.

**Internal Excitatory Signaling May Sensitize Systems**

The FFFS is a system that mediates all aversive stimuli, conditioned and unconditioned (Corr, 2008). One may extend this definition as valid for intrinsic, as well as extrinsic stimuli. A diminished RPE signaling (Adleman et al., 2011) may neurally represent a form of confusion, in that it gives insufficient neural responding to omission of reward. This may be processed as an intrinsic threat signal. If this indeed happens, there is maladaptive neural BAS - FFFS interaction, which in turn may sensitize the FFFS. Furthermore this may lead to further sensitizing of the BIS, in that deficient learning processes constantly constitute a signaling conflict. An approach that is hindered, according to the RST definition, will activate the BIS, and evaluate whether escape (FFFS) is preferential responding (Corr, 2008). A general reward learning deficit as seen with decreased RPE signaling may therefore create hyperactive signaling in both BIS and FFFS.

An understanding of neural conditioning can give some insight into system interactions. Johansen et al. (2010) demonstrated how during the pairing of an unconditioned stimulus with a conditioned stimulus in a fear-conditioning paradigm, neural reaction in the amygdala decreased during early conditioning, and remained so during further trials. This is a case of habituation. In the case of DMDD it may be that children with sensitive FFFS systems, or RPE difficulties constantly signaling threat, sensitizes the BIS system, so that anxiety may result over time. This is certainly a hypothesis in line with the observation that
anxiety and depression predominates later in life for people with DMDD pasts (Copeland et al., 2014).

**A General Model for Testing DMDD**

Brotman et al. (2017) suggested two hypotheses for testing the etiology of childhood irritability. Hypothesis one was rooted in positive feedback loop thinking. Frustration disturbs affect and attention, which again disturbs reward processing, again leading to further frustration. Secondly, an accumulative learning model, in which anticipatory frustration is a response to previous frustrating events, was proposed. Model 1 provides a general experimental design outlay, inspired by the RST, for how to examine DMDD. Here the arrest of a pleasurable activity is hypothesized to increase FFFS signaling and BIS signaling, and BAS sensitive may be expected to have increased show of anger (Carver & Harmon-Jones, 2009). Top-down processes may also be examined through this model.

**Model 1**

*Suggested paradigm set-up for testing the RST in irritable children*

Using this general model to test DMDD neural sensitivity, requires experimental adaptation of the model, time-line fMRI designs, and whole-brain studies. Diffusion tensor imaging (DTI) may reveal the interplay between systems. The mapping of signaling is made possible through this technology, providing a systems interaction design.

**The Anterior Cingulate Cortex is Central in Understanding DMDD**

As noted above, the exact role of the cortex is yet to be established in the RST. The anterior cingulate cortex (ACC) has been hypothesized to be the receptive region for
experiencing emotion (Gray and McNaughton, 2000). BIS is a system of detecting and solving conflict, and the ACC being a part of BIS, it has also been hypothesized to be the region involved in discriminated avoidance (Gray & McNaughton, 2000). The ACC has experimentally been found to have a role in error monitoring (Gehring & Fenzik, 2001, in Margulies et al., 2007) and response selection (Awh & Gehring, 1999, in Margulies et al., 2007). Excessive error monitoring is one of the highly sensitive BIS individuals’ maladaptive functions. In several of the studies cited in this text, an irritability-specific difference in ACC activation has been reported, suggesting its significant role in childhood irritability. Therefore specific analytic focus will be placed on this structure.

**Initial Hypotheses**

Perlman et al. (2015) showed for irritable children compared to healthy controls an increased ACC activation during reward, as well as a decreased ACC activation upon nonreward. It seems that neural ACC activation signals discrepancy in the irritable brain to a greater degree than in the more adaptively functioning brain. There are also BIS-related studies suggesting BIS to be related to ACC activation. Eisenberger et al. (2005) found that neuroticism (BIS) was related to increased dorsal ACC activation in discrepancy detection. BAS may also be represented in the ACC, in that there are associations between ACC and externalizing behavior. For example, Roy, DeSerisy, Bennett, Castelanos and Klein (2017) reported an association between anger outbursts and disruptions in dorsal ACC circuitry. Bledsoe, Semrud-Clikeman and Pliszka (2013) found that ADHD reported degree of severity was related to thinning of right rostral ACC surface. The BIS and the BAS may be involved in ACC activation, and differential activation may underlie irritability. However, the specific topographic signature and connectivity within the ACC is yet to be mapped.

There seems to be age and diagnosis effects on ACC activation (Perlman et al., 2015; Rich et al., 2011). Tseng et al. (2019) measured neural activation on an attentional event immediately after frustration induction, and found that activation of the ACC varied with levels of cross-diagnostic irritability and participant age. The younger participants (aged 8-14) had increased ACC activation together with increased irritability. This pattern was not found in youth aged 14-18. The ACC may be a central structure that matures throughout childhood. A further examination of the role of the ACC in childhood irritability with a focus on different ages and different primary diagnoses is needed in order to assess how it may be involved.

**Experimental Paradigms Testing ACC Involvement**

Deveney et al. (2013) found that self-reported frustration in SMD was related to reduced ability to shift spatial attention. Najmi, Kuckertz and Amir (2012) found that highly
anxious individuals presented with difficulty expanding their attention. Prabhakaran, Kraemer and Thompson-Schill (2011) extended these results with an inhibition task, finding that a BAS-related construct was related to verbal performance, whereas a BIS related measure was related to longer reaction times on a visual test. Heightened BIS seems to have specific influence on visual attention, and the ACC may be central in trying to understand this possible effect. Carver and Harmon-Jones (2009) reviewed the evidence from the RST model, suggesting a lateralization of neural function towards the BIS being right-centered and having relevant effects on spatial analysis, while the BAS is left-centered, possibly related to verbal ability. There is reason to examine whether children with DMDD have a specific visual deficiency, and how the ACC might be involved.

A DMDD neural similarity with borderline personality disorder (BPD) has been hypothesized earlier in this paper, through having hyperactive BIS and BAS (BIS+/BAS+) as underlying trait factors. In a study of BPD reaction to outcome uncertainty, Mortensen et al. (2016) found that BPD participants responded more impulsively on invalid trials, and also exhibited slower responses on neutral trials. There was increased dorsal ACC activity during cues, suggesting strong neural readiness. However, this activity was followed by less precise task responses, so the ACC activation may be related to impulsiveness and BAS reactivity. Behavioral restriction on neutral trials may have been related to BIS activation. While this task resembles previously reported tasks (Rich et al., 2007; 2011), there is need for further examination of outcome uncertainty also in children with DMDD. Uncertainty being a feature of life, this task may be of special interest with children with DMDD. It is possible that DMDD anger expression may be an outcome of a cognitive inflexibility mediated by aberrant ACC activation.

**The ACC May Act as a Switchboard**

One of the major questions within the RST tradition is regarding subsystems interaction (Corr, 2002; McNaughton & Corr, 2004). Structural and functional mapping can provide some provisional guidelines into this, and the ACC is also of special interest here. For the RST, Kennis et al. (2013) suggested the ACC to be a part of the volitional control system, rather than the BIS. They also placed ACC within the FFFS system, coupling fear-related behaviors to ACC activation. Etkin, Egner and Kalish (2011) found that dorsal–caudal regions of the ACC are involved in appraisal and expression of negative emotion. Ventral–rostral parts of the ACC were reviewed as having a regulatory role with respect to limbic regions involved in generating emotional responses. Both BIS and BAS may underlie appraisal and expression of negative emotion, while BIS and EF are possible candidates for regulation in
ventral-rostral parts. FFFS involvement may be involved if the ACC signals a state of readiness, as was hypothesized in the Yu et al. (2014) study.

Margulies et al. (2007) also reported a distinction between ACC rostral affective and dorsal-caudal attention networks (Margulies et al., 2007). Of importance here, the activation of these systems was negatively related. Here the matter of top-down vs bottom-up processes seems relevant, and people with affective disorders may have different ACC functioning. In theory, being irritable, may compromise attention and cognitive functions. The view that ACC acts as a switchboard may be relevant (Beauregard et al., 2004, in Meyers et al., 2017). It is possible that the RST dimensions BIS, BAS, FFFS and EF are all presented in the ACC, and that the ACC has a central role in switching between systems, ensuring best allocation of neural resources and behavioral response. There is reason to attempt to subdivide the ACC in imaging studies in order to understand its role in irritability and how RST systems interaction may fail for children with DMDD.

**ACC Summary of Hypotheses**

The preceding section presented some research on the ACC, placing it in a hypothetically central position in the RST and in the difficulties experienced by irritable children. ACC engagement in ADHD, BPD and in BIS related activation was noted, as well as results reported in this paper on childhood irritability. The ACC may act as a switchboard between RST systems. ACC deficiency in irritable children may be due to bottom-up system reactivity, leading to non-inhibited behavior and aggression, possibly together with ACC-mediated visual attentional deficits. This may be due to FFFS, BIS and BAS being hypersensitive, so that uncertainty will be handled inefficiently, and top-down control may be compromised.

**Children with DMDD May Have Diminished Executive Control**

One of the more pragmatic research questions in this paper is whether one can specify a pattern of neurocognitive deficiency as a part of the DMDD clinical presentation. Neuropsychological testing involves testing intelligence, attention, executive function (EF), social cognition and praxis (Zwick, 2017). In the extended RST model there has been specific focus on EF (Kennis et al., 2013). Miyake et al. (2000) found three main factors to subserve EF; working memory, inhibition and switching. These factors are also proposed for testing the constraint system of the RST (Kennis et al., 2013), as well as a dimension of the cognitive system of the RDoC (Cuthbert & Insel, 2013).

While utilizing the executive functions, neural activations are mainly reported as focused in areas of the cortex (Miyake, 2000). EFs are believed to be primarily prefrontal
functions. Working memory (WM) requires sustained attention, as well as updating information. Having information online in WM aids in conscious decision making. Inhibition requires stopping a predominant or automated response in order to keep focus on a task. Switching requires the alternation of attentive resources to different rules or types of stimuli, and is also measured in tasks on cognitive flexibility. As a prerequisite of higher level control, attention is essential and can be examined in various ways. Initial and sustained attention require different neural resources (Rich et al., 2007). While performance on EF tasks is a cognitive measure, there is also a proposed link between executive functioning and self-regulation ability (Hofmann et al., 2012). Whether different clinical presentations may have specific or generalized EF domain difficulties, is an important research question.

Seeing that there is altered ACC functioning in children with SMD, opens up for theorizing about how this may affect higher cognitive functioning. The reports above have shown differential neural activation between irritable children and other groups (e.g. Adleman et al., 2011; Kessel et al., 2016; Perlman et al., 2015; Rich et al., 2007; 2011). However, children with DMDD or other type of irritability have often performed equally well on neuropsychological tasks to other groups, including healthy controls (Pagliaccio et al., 2017; Rich et al. 2011; Taskiran et al., 2017). Rich et al. (2007) though, discovered a specific SMD difficulty with initial attention, while Pagliaccio et al. (2017) found a DMDD/ADHD severity-dependent difficulty with sustained attention. Tseng et al. (2019) found no performance differences due to irritability, but reported neurological compensatory mechanisms during a post-frustration attention task. This means that non-imaging studies may not discover any difference between irritable children and other clinical groups. However, it may be that the level of irritability as a continuous variable is necessitated in research designs. Level of irritability was negatively related to performance on a task of sustained attention (Pagliaccio et al., 2017).

Tseng et al. (2019) provided an example of greater recruitment of the EF after frustration induction, through ACC and dorsolateral PFC activation, in a sample of children and youth having a degree of irritability, including a DMDD group. There seems to be a greater need for higher control functions when emotionally aroused, specifically the area needed for updating working memory. This may signify that irritability has increased bottom-up signaling so that the PFC needs constant updating, requiring additional neural effort. Also, of note in this study, striatal activation was positively related to irritability, signifying BAS involvement. This involvement is conducive to a readiness to engage. Frustration-inducing tasks or tasks of emotional relevance are called hot EF tasks, whereas tasks assumed to be
cognitive and non-emotional, are called cool tasks. The Tseng et al. (2019) initial task was hot, while the following task was cool. When emotionality was induced, additional top-down regulation by the PFC was seen.

In the RST the EF has been conceptualized as a top-down control system upon the other systems (Kennis et al., 2013). A bottom-up and top-down interplay of function is likely, so engaging one system may signal downregulation on another, just as was found locally in the ACC (Margulies et al., 2007), referred to earlier in this paper. In a normal population periaqueductal grey (PAG) activation was found to be greater in more complex cognitive control tasks. This activation resulted from cortical signaling to the PAG, and suggested to underlie an adjustment of sympathetic resources (Kragel et al., 2019). For irritable children this function may be compromised. Tseng et al. (2019) found that left IFG – PAG connectivity was reduced in irritable children. The PAG being a part of the FFFS (Corr, 2008), and the IFG being needed for response inhibition (Adleman et al., 2011), makes this result important in understanding irritability in terms of the RST model. For irritable children, aspects of top-down control may be diminished, as seen here with reduced connectivity. Bottom-up signaling may take precedence, and as such increase emotional and behavioral impulsivity. Upregulation of arousal may also be the effect when top-down control is inefficient, so that neural signals may induce a feeling of uneasiness or unrest, or even anxiety.

Bunford, Roberts, Kennedy and Klumpp (2017) studied neural activation during stimuli with either low or high perceptual load in a normal population. Participants were asked to press a button when they saw a target letter superimposed on a face, either in a string of identical letters or in a string of various letters. They found that BIS-sensitive under low perceptual load showed increased dorsolateral PFC activation in response to angry distractor faces, and dorsal ACC activation to fearful faces. Under high perceptual load, there was no difference in neural activity between high and low BIS groups. This suggests that BIS sensitivity is mirrored in neural processes related to the valence of emotional stimuli. However, when needed in this healthy sample, top-down processing took precedence. People seem to become focused on the task rather than the distractor, so that individuals are primed to task performance. Whether children with DMDD, hypothesized to have a hypersensitive BIS, would show the same switching between systems, depending of task requirement, is a question for future research. In ecological settings this seems to be one of the struggles of children with DMDD.
Cognition is measured in innumerous ways, and conceptual clarity about what aspect of cognitive control that is measured is needed. Hung, Gaillard, Yarmak and Arsalidou (2017) conducted a review of different types of inhibition. Cognitive inhibition, response inhibition and emotional interference were all found to rely on the anterior insula. In addition, separate neural systems are involved depending on paradigm. Given that inhibition difficulty is a part of the clinical picture for children with DMDD, this concept needs some examination and clarity. For motor inhibition, no behavioral difference between severe mood dysregulation (SMD), bipolar disorder (BD) and healthy controls (HC) was found (Deveney et al., 2012). However, neural activation of the right ACC and right nucleus accumbens was greater only in BD youths during failed inhibition, suggesting a normative motor inhibition capacity for the SMD group. Whether this result will persist in studies on children with DMDD remains to be seen. SMD cognitive inhibition difficulties were found in the Adleman et al. (2011) study of reversal learning. While reversal learning measures cognitive flexibility, when task condition changes, prepotent learned response also needs inhibition. SMD participants were found to have significantly less correct trials than BD and HC (Adleman et al., 2011). A reversal learning paradigm with children with DMDD, should be replicated, also including a measure of severity. Performance on pure cognitive control tasks must also be assessed.

The studies attempting to establish DMDD measures on cool EF tasks have been confounded by ADHD comorbidity (Adleman et al., 2011; Pagliaccio et al., 2017; Taskiran et al., 2017). In a population-based study, Blanken et al. (2017) found that in a combined internalizing/ externalizing group, which they called the “dysregulated” group, there was variability in performance across executive functioning domains. This result may signify that one cannot find a cognitive profile in cool measures of children with DMDD, to be used deductively in clinic. These children did, however, have an 11-point lower average on a non-verbal intelligence scale, which may be in line with the previously stated hypothesis that children with DMDD may struggle with visual attention. Blanken et al. (2017) also found a specific sensori-motoric difficulty to be a feature of the dysregulated group. They had made measures to exclude children fulfilling ASD criteria. Their stated study limitation, however, was that they were unsure whether the results may have been due to them testing a group of high functioning ASD. Another limitation was that they only used one pencil and paper test from which they acquired these results. If there is a sensori-motoric difficulty in children with DMDD, all tasks requiring the coordination of response may be relevant.

The final inhibition domain of the Hung et al. (2017) article was that of emotional interference. It was conceptualized as a ventral inhibitory system. The inferior frontal gyrus is
implicated in this system (Hung et al., 2017), and Adleman et al. (2011) found that participants had lessened difference in IFG activation when subtracting correct from incorrect trials, suggesting a specific neural processing deficit in terms of deficient inhibition for SMD. Adleman et al. (2011) did not reflect on emotions, rather on response selection and attention maintenance. However, there is a possibility that emotional reactivity to task was involved in SMD participants, due to their general emotional reactivity. Frustration paradigms have been reported frequently throughout this paper with regards to irritable children, suggesting lower tolerance for nonreward, and suggesting neural top-down compensation mechanisms (e.g. Pagliaccio et al., 2017; Rich et al., 2007; 2011; Tseng et al., 2019). In one study, the SMD group showed impairment in spatial attention shifting ability while being frustrated (Deveney et al., 2013). Furthermore, frustration-induced attentive control deficits result in emotion regulation difficulties and externalizing behavior (Gatzke-Kopp et al., 2015). Due to differing performance results (Rich et al., 2007; 2011), the effects of irritability may go undetected in a normal test situation. In clinic, without fMRI, neural emotional interference may not be strong enough to provide a measure of irritability. The challenge here for researchers would be to design a neuropsychological test that could validly distinguish between children with DMDD and other presentations, also without fMRI.

The central hypothesis with regards to DMDD in this paper is that the inhibition domain of emotional interference may be most predictive of cognitive difficulty. As mentioned previously, emotional interference may have an effect on visual attention. Taskiran et al. (2017) finding DMDD/ADHD difficulty on the TMT task is another piece of evidence that supports the hypothesis of an emotion-activated visual attention diminishment effect. The reading of neutral and ambiguous faces as hostile (Stoddard et al., 2016), may also be related to emotion related visual attention deficits or biases, based in a hyperactive FFFS and BIS. Ecologically, it is evident that children with DMDD do not handle frustration well. For frustration paradigms to differentiate between DMDD and other conditions behaviorally, more real-life paradigms are suggested. With regards to examining DMDD performance on cool measures of EF, strict diagnostic separation and large research groups are needed.

**Section Summary**

In understanding irritability, it has been suggested here that the threat system may be essential, as a highly sensitive part of the nervous system in irritable children. The proposition that nonreward may elicit an intrinsic and nonconscious alarm signal which may elicit and sensitize other neural systems has been forwarded. Bottom-up neural sensitivity was proposed to have an effect on top-down control processes, and more research on this interaction is
suggested. Furthermore, the ACC may have a switching role, in that all the RST systems may be represented in subdivisions of the ACC. Bottom-up emotionality has been suggested to have an effect on visual attention both with regards to performance on tasks requiring visual attention and in the interpretation of ambiguous social stimuli. For cool EF tasks, there may be little effect of DMDD on performance, due to the non-emotional nature of tasks. However, it is yet to be discovered whether or not an ACC-mediated visual attention deficit may be a feature of children with DMDD, and whether it is related to the emotional processing of stimuli. More research on hot and cool executive functioning of children with DMDD is needed, in order to further the preliminary understanding of the cognitive functioning of children with the DMDD diagnosis.

Limitations and Future Directions

It is an extensive and ambitious task to evaluate the usefulness of the RST in terms of providing a neurologic explanation of DMDD. In RST research on psychopathology there has been emphasis on the BIS and the BAS (Bijttebier et al., 2009). Being non-conform to leading RST research on psychopathology, in this paper the involvement of the FFFS has been highlighted as a possible sensitive system in childhood irritability. Due to this proposition, this paper has focused on a thorough investigation of this. Furthermore a combined sensitivity of bottom-up neural signaling has been proposed. The thorough treatment of other aspects of the RST has been left out to the benefit of the analysis of the FFFS. Specifically, the BAS with its four components; wanting, striving, incentive motivation and liking, each with corresponding neurochemical correlates (Krupić & Corr, 2017), has been undertreated in the present paper. While a reward signaling deficit has been found (Adleman et al., 2011; Kessel et al., 2016), little emphasis has been made to further the exploration of the BAS. There are many open questions with regards to FFFS/ BIS interaction, as well as total systems interaction in childhood irritability. This paper has opened up for the further analysis of such questions.

Kennis et al. (2013) defined a fourth factor of the RST, with the underlying structures of the ACC and the PFC; constraint. In this paper a specific emphasis has been put on evaluating the ACC, at the cost of focus on other neural structures. The ACC having a hypothetical switching function between emotional reactive control and more rational control, as well as in reflexive system interaction, this focus has been necessitated. However, valuable information regarding systems interaction from cited studies has been down-prioritized due to the focus on the ACC. This approach is counterintuitive. For the RST it is the total system
involvement that is of interest, made possible through imaging studies, if one is to evaluate the feasibility of the model. However, due to the ACC not yet having been fully incorporated into the model (Gray & McNaughton, 2000), this is seen as a first step in aiding the understanding of irritability and in aiding the provision of the seeds to an extension of the model.

In Kennis et al.’s (2013) definition of the fourth factor they included the term *volition*, and then reduced and operationalized this factor to executive functioning, being assessed in tasks accessing working memory, inhibition and switching. However, *volition* in neuropsychology may be seen as more of a philosophical concept than an experimental one (e.g. Frith, 2013). Carver (2005) discussed models distinguishing between a rational and an experiential system, however none of these included the Gray focus on neurology as a mirror of actions. In this paper the reflective parts of human behavior have not been examined, mostly as it is the reflexive aspects that have been studied in experimental paradigms. Tasks requiring top-down control are believed here to be reflexive the moment they have been automatized. It is during the acquisition phase and during failure that more reflection might be activated. The non-treatment of reflection may be a weakness of the RST model. Also the aspect of reflection may be incorporated at a later stage, once the reflexive processes have been mapped.

Frith (2013) discussed the concept of *volition*, neurologically placing free choice in the dorsolateral PFC. In this specific area, the neocortex undertakes action selection from competing possibilities. He distinguished between predictable and unpredictable behavior. In instrumental conditioning choice is made upon expected outcome, making this choice more predictable than in more complex situations. However instrumentality exists everywhere in life. The possible instrumentality of childhood irritability has not been covered in this paper. The manifestation of irritability may also be instrumental, as a learned response. If a sensitive child is overly stimulated, possibly having an anger outburst may result in the peace that the child requires. They may not have the awareness of this need, nor have the ability to communicate it, but an anger outburst may result in a needed quiet after the outburst due to parents withdrawing from the communication.

An interaction between neural sensitivity and the environment has been suggested in this paper. Transactional developmental theories are certainly valuable in understanding DMDD, as child neural vulnerability may challenge parents, other caretakers and peers. Normal parenting strategies and other environmental responses to the sensitive child may also be inadequate and possibly reinforcing problems and neural sensitivity. While there are
reports on childhood trauma altering neural volumes and functional connectivity (De Souza Queiroz et al., 2015), this paper has explicitly not dealt with this aspect of development. Very little is known about childhood conditions for children with DMDD. This focus is clearly needed. However, in this paper the specific focus has been on neural systems involvement regardless of ecological input, and model development.

For further research on the propositions forwarded in this paper, several study designs have been suggested. Generally, larger diagnostic groups are needed, where specifically a group of DMDD without attention difficulties, if possible, needs evaluation. The tasks should attempt to establish possible deficiencies in both cool and hot executive measures. Different types of inhibition, including motor and cognitive inhibition, as well as inhibition of emotional interference need testing in separate study designs. In order to test interaction between RST systems, whole-brain fMRI timeline designs are needed. This includes research on top-down and bottom-up control mediated by the ACC. A general model has been proposed as to how to do this. More ecologically relevant studies on threat have been suggested, as well as more basic research on early neural reactivity possibly predisposing for DMDD pathology.

**Concluding Remarks**

Disruptive mood dysregulation disorder is a newly conceptualized disorder, and thus in need of scrutiny in terms of presentation, differential diagnostic boundaries as well as possible overlap with other disorders. The present paper is in line with the RDoC, trying to establish one possible neurobiological explanation of DMDD. The RDoC domains of specific importance here have been the negative valence domain (threat), some focus on reward sensitivity as grouped under the positive valence domain, as well as parts of the cognitive domain (EF). In RST terms, hypersensitive FFFS, BIS and BAS, as well as possibly diminished top-down control (EF) have been proposed as the neural sensitivity constitution of children with DMDD. This combination of sensitivities are hypothesized to be a vulnerability factor in the development of DMDD, and is a rare and grave form of combined sensitivities according to RST research (Bijttebier et al., 2009; Soler et al., 2014). Accentuating the FFFS as a factor in psychopathology outside of panic and phobias is a new endeavor in the clinical research domain using the RST.

Summing up the research propositions above, there is need for a top-down, bottom-up, and a switching focus in research on DMDD. A larger focus on the FFFS in the RST research tradition in general may be warranted, as well as research evaluating the separate
contributions of the BIS and the FFFS. The ACC has been hypothesized to be central in the switching between FFFS, BIS, BAS and EF, and is in need of specific focus if this structure is to be incorporated fully in the RST paradigm. Understanding the ACC functional divisions is of interest when disseminating the neural mediators of irritability. There is reason to believe that children with DMDD have greater threat sensitivity, possibly contributing to anxiety short and long-term. A reward prediction error signaling deficit is also proposed to underlie increased threat signaling and frustration.

On a clinical note, the prefrontal compensation mechanisms seen in studies, lays the ground for the advice of giving these children sufficient rest. There is convincing evidence that irritability requires compensatory top-down control mechanisms for children to function adequately. Due to this compensatory prefrontal activity there is reason to believe that children with DMDD tire more easily, and that making room for more breaks, as well as reducing amount of stimuli, will aid everyday functioning to a certain degree. While this need is not exclusive to DMDD, the present paper has indicated the neural processes specific to childhood irritability that may account for an over-activation of cognitive processes, both as bottom-up and top-down processing have been found to be greater than in other populations.
Reference List


